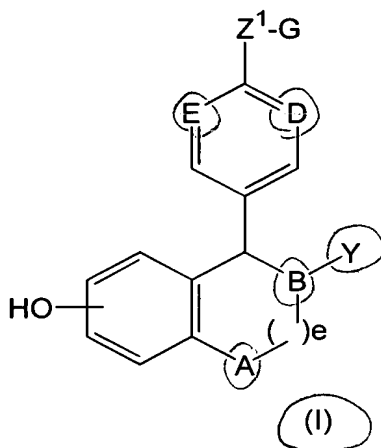


Claims:

Group I
Sub A
1. A method for treating female sexual dysfunction comprising:
administering to a female subject in need thereof, an effective amount of an
estrogen agonist / antagonist, and optionally,
co-administering an effective amount of a cyclic guanosine 3',5'-
monophosphate elevator.

2. A method as in claim 1 wherein said estrogen agonist / antagonist of the
following formula (I):



wherein:

A is selected from CH₂ and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents
independently selected from R⁴;

(b) naphthyl, optionally substituted with 1-3 substituents
independently selected from R⁴;

(c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents
independently selected from R⁴;

(d) C₃-C₈ cycloalkenyl, optionally substituted with 1-2
substituents independently selected from R⁴;

(e) a five membered heterocycle containing up to two
heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally
substituted with 1-3 substituents independently selected from R⁴;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n- optionally substituted with 1-3 substituents independently selected from R⁴; or

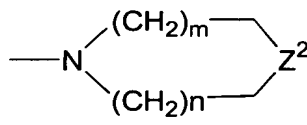
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

Z¹ is

- (a) -(CH₂)_p W(CH₂)_q-;
- (b) -O(CH₂)_p CR⁵R⁶-;
- (c) -O(CH₂)_p W(CH₂)_q-;
- (d) -OCHR²CHR³-; or
- (e) -SCHR²CHR³-;

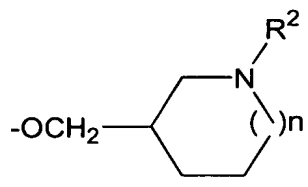
G is

- (a) -NR⁷R⁸;



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R⁴; or



Z¹ and G in combination may be
W is

- (a) -CH₂-;
- (b) -CH=CH-;
- (c) -O-;

(d) $-\text{NR}^2-$;

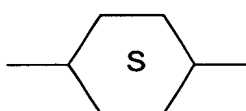
(e) $-\text{S(O)}_n-$;

(f) $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—}$;

(g) $-\text{CR}^2(\text{OH})-$;

(h) $-\text{CONR}^2-$;

(i) $-\text{NR}^2\text{CO}-$;

(j)  ; or

(k) $-\text{C}\equiv\text{C}-$;

R is hydrogen or $\text{C}_1\text{--C}_6$ alkyl;

R^2 and R^3 are independently

(a) hydrogen; or

(b) $\text{C}_1\text{--C}_4$ alkyl;

R^4 is

(a) hydrogen;

(b) halogen;

(c) $\text{C}_1\text{--C}_6$ alkyl;

(d) $\text{C}_1\text{--C}_4$ alkoxy;

(e) $\text{C}_1\text{--C}_4$ acyloxy;

(f) $\text{C}_1\text{--C}_4$ alkylthio;

(g) $\text{C}_1\text{--C}_4$ alkylsulfinyl;

(h) $\text{C}_1\text{--C}_4$ alkylsulfonyl;

(i) hydroxy ($\text{C}_1\text{--C}_4$)alkyl;

(j) aryl ($\text{C}_1\text{--C}_4$)alkyl;

(k) $-\text{CO}_2\text{H}$;

(l) $-\text{CN}$;

(m) $-\text{CONHOR}$;

(n) $-\text{SO}_2\text{NHR}$;

(o) $-\text{NH}_2$;

(p) $\text{C}_1\text{--C}_4$ alkylamino;

(q) $\text{C}_1\text{--C}_4$ dialkylamino;

(r) $-\text{NHSO}_2\text{R}$;

- (s) $-\text{NO}_2$;
- (t) $-\text{aryl}$; or
- (u) $-\text{OH}$;

R^5 and R^6 are independently $\text{C}_1\text{-C}_8$ alkyl or together form a $\text{C}_3\text{-C}_{10}$

5 carbocyclic ring;

R^7 and R^8 are independently

- (a) phenyl;
- (b) a $\text{C}_3\text{-C}_{10}$ carbocyclic ring, saturated or unsaturated;
- (c) a $\text{C}_3\text{-C}_{10}$ heterocyclic ring containing up to two heteroatoms,

10 selected from $-\text{O}-$, $-\text{N}-$ and $-\text{S}-$;

- (d) H ;
- (e) $\text{C}_1\text{-C}_6$ alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R^5 or

R^6 ;

15 R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from $\text{C}_1\text{-C}_6$ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

20 m is 1, 2 or 3;

n is 0, 1 or 2;

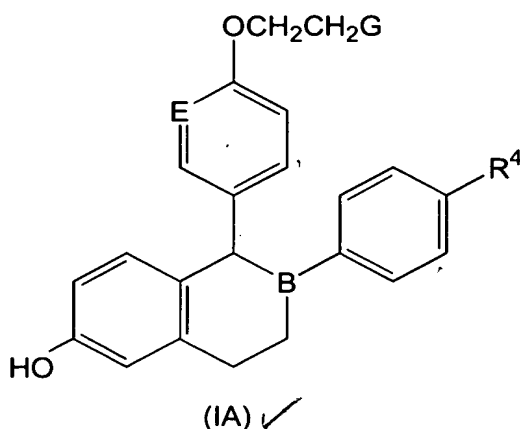
p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable

25 salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

3. A method as in claim 2 wherein said estrogen agonist / antagonist is a compound of formula (IA):



5 wherein G is



R⁴ is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

15

4. A method as in claim 3 wherein said estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

20

5. A method as in claim 4 wherein said estrogen agonist / antagonist is in the form of a D-tartrate salt.

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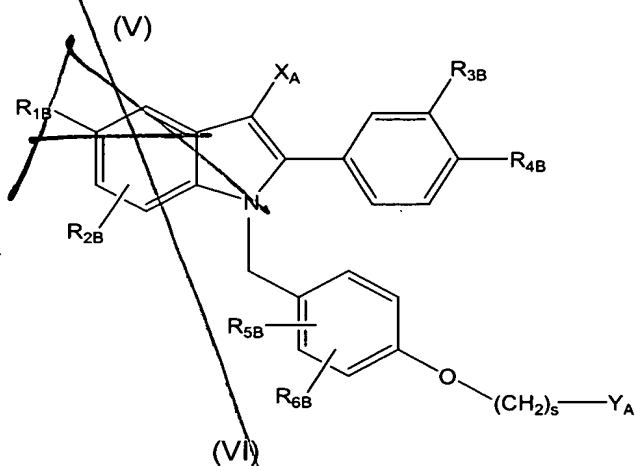
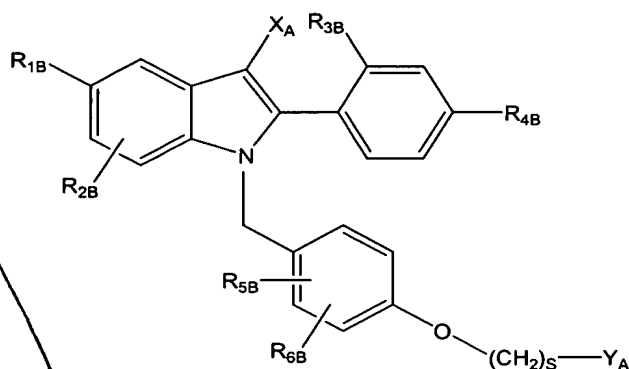
6. A method as in claim 1 wherein said estrogen agonist / antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, raloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, 4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl]-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

30

G = pyrrolidinyl
B = C
E = C

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specie

7. A method as in claim 1 wherein said estrogen agonist / antagonist is a compound selected from the formulas V or VI:



wherein:

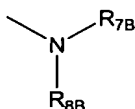
R_{1B} is selected from H, OH, $-O-C(O)-C_1-C_{12}$ alkyl (straight chain or branched), $-O-C_1-C_{12}$ alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers,

R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} are independently selected from H, OH, $-O-C(O)-C_1-C_{12}$ (straight chain or branched), $-O-C_1-C_{12}$ (straight chain or branched or cyclic), halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_{1B} is H, R_{2B} is not OH;

X_A is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

5 Y_A is the moiety:



wherein:

10 a) R_{7B} and R_{8B} are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; or

15 b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B},
20 -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B},
25 -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

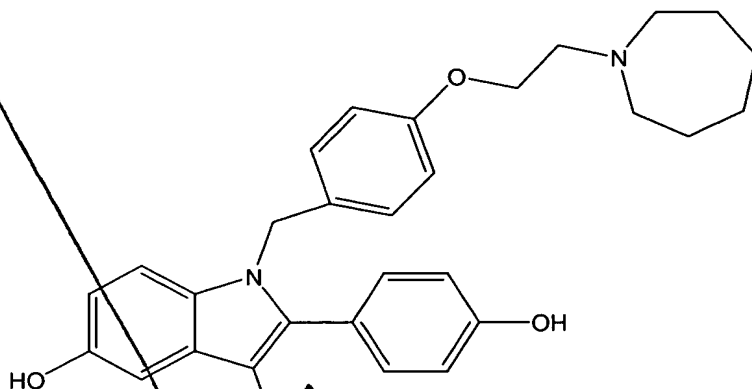
30 d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl,

-CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂ R_{1B},
-NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle
5 containing one nitrogen heteroatom, the heterocycle being optionally substituted with
1-3 substituents independently selected from the group consisting of hydrogen,
hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄
acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl,
-CO₂H, -CN, -CONHR₁, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B},
10 -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing
from 6-12 carbon atoms either bridged or fused and containing one nitrogen
heteroatom, the heterocycle being optionally substituted with 1-3 substituents
15 independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄
alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-
C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂ H, -CN, - CONHR_{1B},
-NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl
optionally substituted with 1-3 (C₁-C₄) alkyl; or an optical or geometric isomer thereof;
20 or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or
prodrug thereof.

8. A method as in claim 7 wherein said estrogen agonist / antagonist is the
compound, TSE-424, of formula Va below:

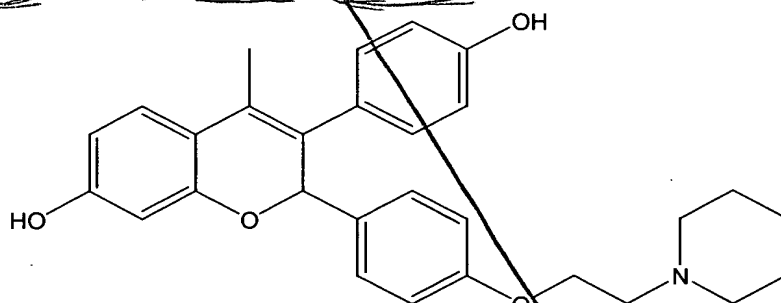


(Va) ✓

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

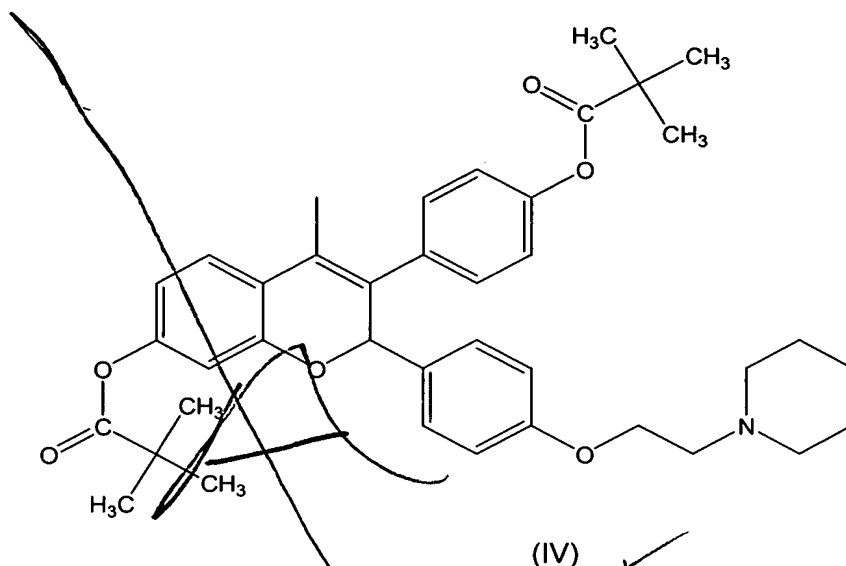
5

9. A use as in claim 1 wherein said estrogen agonist / antagonist is EM-652 of formula III below or is EM-800 of formula IV below:



(III) ✓

10



5 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

10. A method as in claim 1 further comprising co-administering a cyclic guanosine 3',5'-monophosphate elevator.

10

11. A method as in claim 8 wherein said cyclic guanosine 3',5'-monophosphate elevator is a PDE_v phosphodiesterase inhibitor.

12. A method as in claim 5 further comprising co-administering 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate salt.

15

13. A method as in claim 1 wherein said method substantially reduces the concomitant liability of adverse effects associated with estrogen administration.

20

14. A method as in claim 1 wherein said female sexual dysfunction is a condition selected from the group consisting of hypoactive sexual desire disorder, sexual arousal disorder, dyspareunia and vaginismus.

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specie
elect one
ultimate disorder
(1) cl 14 is (2) disorders

Group II

15. A kit for use by a consumer to treat female sexual dysfunction comprising:

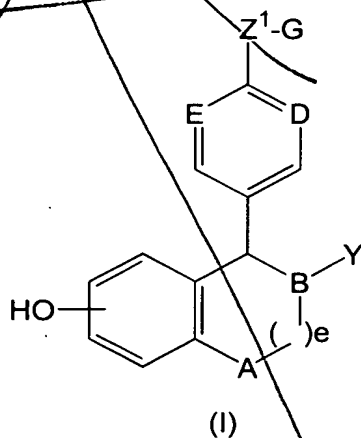
(a) a pharmaceutical composition comprising an estrogen agonist / antagonist and a pharmaceutically acceptable carrier, vehicle or diluent; and optionally,

5 (b) a pharmaceutical composition comprising a cyclic guanosine 3',5'-monophosphate elevator and pharmaceutically acceptable carrier, vehicle or diluent; and optionally,

(c) instructions describing a method of using the pharmaceutical composition(s) to treat female sexual dysfunction,

10 wherein said estrogen agonist / antagonist and said cyclic guanosine 3',5'-monophosphate elevator may optionally be combined in the same pharmaceutical composition.

16. A kit as in claim 15 wherein said estrogen agonist / antagonist of the following formula (I):



wherein:

20 A is selected from CH₂ and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R⁴;

25 (b) naphthyl, optionally substituted with 1-3 substituents independently selected from R⁴;

(c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents independently selected from R⁴;

(d) C₃-C₈ cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R⁴;

5 (e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n- optionally substituted with 1-3 substituents independently selected from R⁴; or

(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

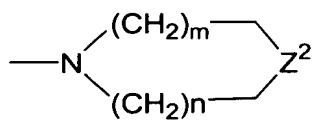
15 Z¹ is

- (a) -(CH₂)_p W(CH₂)_q-;
- (b) -O(CH₂)_p CR⁵R⁶-;
- (c) -O(CH₂)_p W(CH₂)_q-;
- (d) -OCHR²CHR³-; or
- (e) -SCHR²CHR³-;

20

G is

- (a) -NR⁷R⁸;

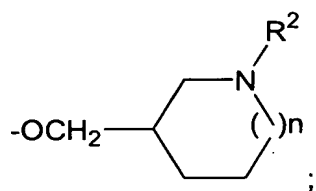


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-;

25 optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents

30 independently selected from R⁴; or



Z¹ and G in combination may be

W is

- (a) $-CH_2-$;
- (b) $-CH=CH-$;
- (c) $-O-$;
- (d) $-NR^2-$;
- (e) $-S(O)_n-$;

- (f) $-\overset{\overset{O}{\parallel}}{C}-$;
- (g) $-C(R^2)(OH)-$;
- (h) $-CONR^2-$;
- (i) $-NR^2CO-$;

- (j) $-\text{C}_6\text{H}_4-S-\text{C}_6\text{H}_4-$; or
- (k) $-C\equiv C-$;

R is hydrogen or C₁-C₆ alkyl;

R² and R³ are independently

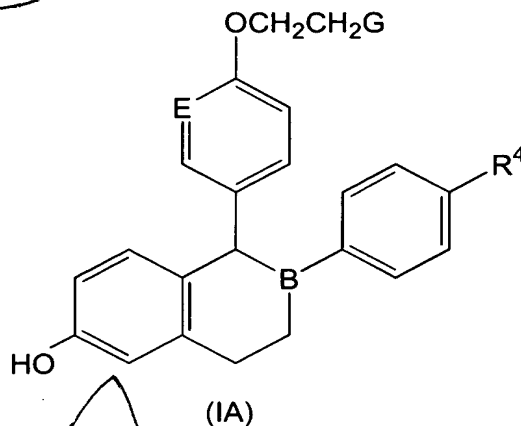
- (a) hydrogen; or
- (b) C₁-C₄ alkyl;

R⁴ is

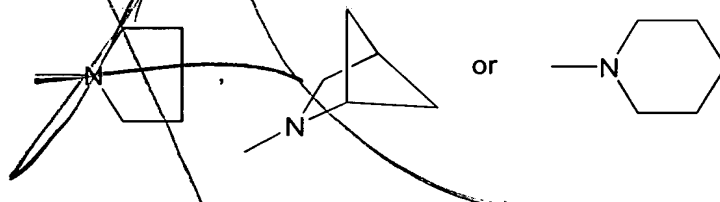
- (a) hydrogen;
- (b) halogen;
- (c) C₁-C₆ alkyl;
- (d) C₁-C₄ alkoxy;
- (e) C₁-C₄ acyloxy;
- (f) C₁-C₄ alkylthio;
- (g) C₁-C₄ alkylsulfinyl;
- (h) C₁-C₄ alkylsulfonyl;
- (i) hydroxy (C₁-C₄)alkyl;
- (j) aryl (C₁-C₄)alkyl;

- (k) $-\text{CO}_2\text{H}$;
 (l) $-\text{CN}$;
 (m) $-\text{CONHOR}$;
 (n) $-\text{SO}_2\text{NHR}$;
 (o) $-\text{NH}_2$;
 (p) $\text{C}_1\text{-C}_4$ alkylamino;
 (q) $\text{C}_1\text{-C}_4$ dialkylamino;
 (r) $-\text{NHSO}_2\text{R}$;
 (s) $-\text{NO}_2$;
 (t) -aryl; or
 (u) $-\text{OH}$;
- R^5 and R^6 are independently $\text{C}_1\text{-C}_8$ alkyl or together form a $\text{C}_3\text{-C}_{10}$ carbocyclic ring;
 R^7 and R^8 are independently
- (a) phenyl;
 (b) a $\text{C}_3\text{-C}_{10}$ carbocyclic ring, saturated or unsaturated;
 (c) a $\text{C}_3\text{-C}_{10}$ heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
 (d) H;
 (e) $\text{C}_1\text{-C}_6$ alkyl; or
 (f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6 ;
- R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from $\text{C}_1\text{-C}_6$ alkyl, halogen, alkoxy, hydroxy and carboxy;
 a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
 e is 0, 1 or 2;
 m is 1, 2 or 3;
 n is 0, 1 or 2;
 p is 0, 1, 2 or 3;
 q is 0, 1, 2 or 3;
- or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

- 3 ≈ 17. A kit as in claim 16 wherein said estrogen agonist / antagonist is a compound of formula (IA):



wherein G is



10

15

R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

- 4 ≈ 18. A kit as in claim 17 wherein said estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

20

- 5 ≈ 19. A kit as in claim 18 wherein said estrogen agonist / antagonist is in the form of a D-tartrate salt.

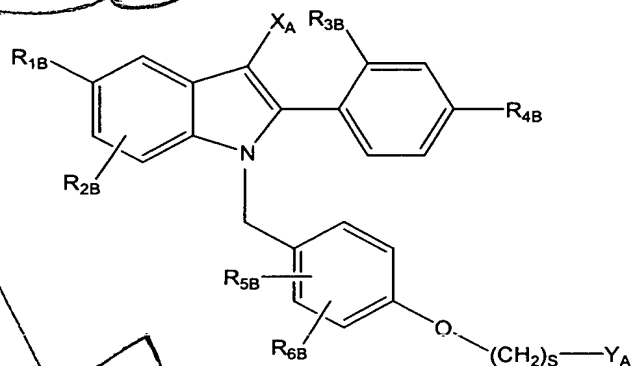
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- 6 ≈ 20. A kit as in claim 15 wherein said estrogen agonist / antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, raloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604 and optical or geometric isomers thereof; and pharmaceutically

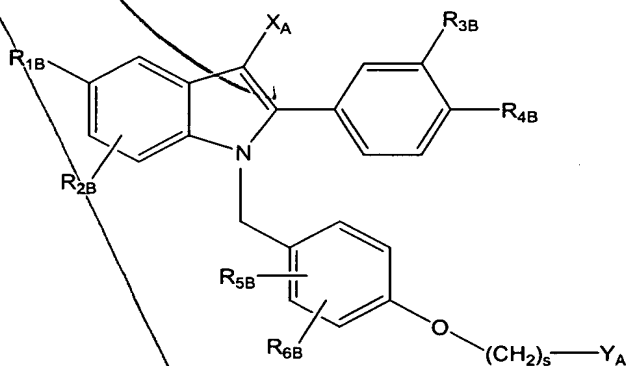
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acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

21. A kit as in claim 15 wherein said estrogen agonist / antagonist is a compound selected from the formulas V or VI:



(V)



(VI)

wherein:

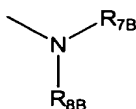
R_{1B} is selected from H, OH, $-O-C(O)-C_1-C_{12}$ alkyl (straight chain or branched), $-O-C_1-C_{12}$ alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers,

R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} are independently selected from H, OH, $-O-C(O)-C_1-C_{12}$ (straight chain or branched), $-O-C_1-C_{12}$ (straight chain or branched or cyclic), halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R_{1B} is H, R_{2B} is not OH;

X_A is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3;

Y_A is the moiety:



wherein:

- 10 a) R_{7B} and R_{8B} are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; or
- 15 b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN-, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, 20 -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, 25 hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- 30 d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl,

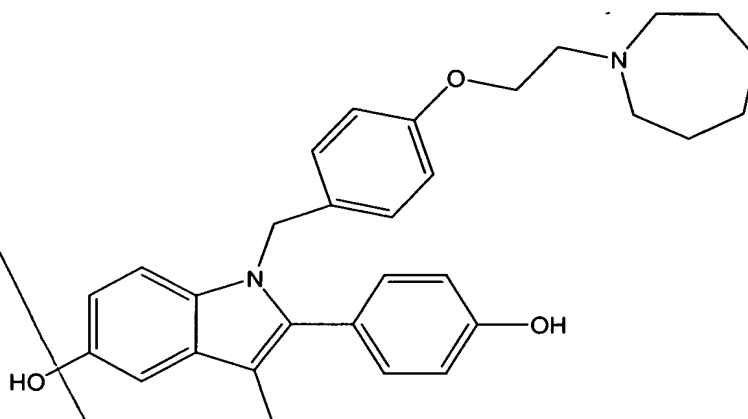
-CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂ R_{1B},
-NHCOR_{1B} -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

5 e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle
containing one nitrogen heteroatom, the heterocycle being optionally substituted with
1-3 substituents independently selected from the group consisting of hydrogen,
hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄
acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl,
10 -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B},
-NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

15 f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing
from 6-12 carbon atoms either bridged or fused and containing one nitrogen
heteroatom, the heterocycle being optionally substituted with 1-3 substituents
independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄
alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-
C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂ H, -CN, -CONHR_{1B}, -
NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl
optionally substituted with 1-3 (C₁-C₄) alkyl;
20 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-
oxide, ester, quaternary ammonium salt or prodrug thereof.

8 ≈ 22. A kit as in claim 21 wherein said estrogen agonist / antagonist is the
compound, TSE-424, of formula Va below:

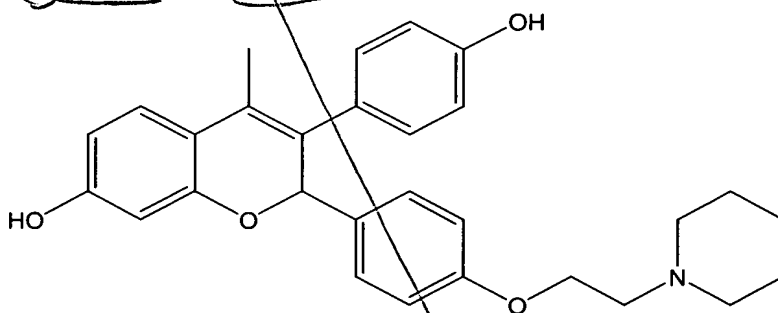
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(Va)

5 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

9 ≈ 23. A kit as in claim 15 wherein said estrogen agonist / antagonist is EM-652 of formula III below or EM-800 of formula IV below:



(III)

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- ✓ (a) an estrogen agonist / antagonist, and
- ✓ (b) a cyclic guanosine 3',5'-monophosphate elevator.

10

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The diagram shows a chemical structure of a substituted benzene ring. The ring is part of a larger system, with a hydroxyl group (HO-) attached to one of the carbons. The ring is substituted with a Z¹-G group, an E group, a D group, and a B-Y group. The B-Y group is shown as a carbon atom bonded to a B atom, which is further bonded to a Y atom. The B atom is also bonded to a group labeled ()_e. The Z¹-G group is shown as a carbon atom bonded to a Z¹ atom, which is further bonded to a G atom. The E group is shown as a carbon atom bonded to an E atom. The D group is shown as a carbon atom bonded to a D atom. The structure is drawn with a perspective view, showing the ring and the substituents in a 3D-like arrangement.

(I)

20

B, D and E are independently selected from CH and N;

25

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R⁴;

(c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents independently selected from R⁴;

(d) C₃-C₈ cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R⁴;

5 (e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴; or

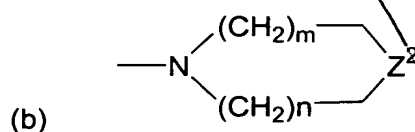
10 (g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

15 Z¹ is

- (a) -(CH₂)_pW(CH₂)_q-;
- (b) -O(CH₂)_pCR⁵R⁶-;
- (c) -O(CH₂)_pW(CH₂)_q-;
- (d) -OCHR²CHR³-; or
- 20 (e) -SCHR²CHR³-;

G is

- (a) -NR⁷R⁸;

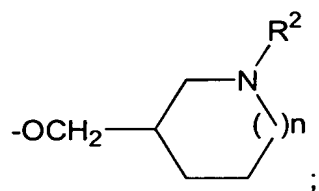


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-;

25 optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R⁴; or

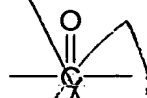
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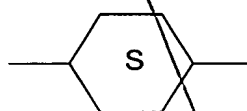


Z¹ and G in combination may be

W is

- (a) -CH₂-;
- (b) -CH=CH-;
- (c) -O-;
- (d) -NR²-;
- (e) -S(O)_n-;

- (f) ;
- (g) -CR³(OH)-;
- (h) -CONR²-;
- (i) -NR²CO-;

- (j) ; or
- (k) -C≡C-;

R is hydrogen or C₁-C₆ alkyl;

R² and R³ are independently

- (a) hydrogen; or
- (b) C₁-C₄ alkyl;

R⁴ is

- (a) hydrogen;
- (b) halogen;
- (c) C₁-C₆ alkyl;
- (d) C₁-C₄ alkoxy;
- (e) C₁-C₄ acyloxy;
- (f) C₁-C₄ alkylthio;
- (g) C₁-C₄ alkylsulfinyl;
- (h) C₁-C₄ alkylsulfonyl;
- (i) hydroxy (C₁-C₄)alkyl;
- (j) aryl (C₁-C₄)alkyl;

- 5
- (k) -CO₂H;
 - (l) -CN;
 - (m) -CONHOR;
 - (n) -SO₂NHR;
 - (o) -NH₂;
 - (p) C₁-C₄ alkylamino;
 - (q) C₁-C₄ dialkylamino;
 - (r) -NHSO₂R;
 - (s) -NO₂;
 - 10 (t) -aryl; or
 - (u) -OH;

R⁵ and R⁶ are independently C₁-C₈ alkyl or together form a C₃-C₁₀ carbocyclic ring;

R⁷ and R⁸ are independently

- 15
- (a) phenyl;
 - (b) a C₃-C₁₀ carbocyclic ring, saturated or unsaturated;
 - (c) a C₃-C₁₀ heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
 - (d) H;
 - 20 (e) C₁-C₆ alkyl; or
 - (f) form a 3 to 8 membered nitrogen containing ring with R⁵ or R⁶;

25 R⁷ and R⁸ in either linear or ring form may optionally be substituted with up to three substituents independently selected from C₁-C₆ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

n is 0, 1 or 2;

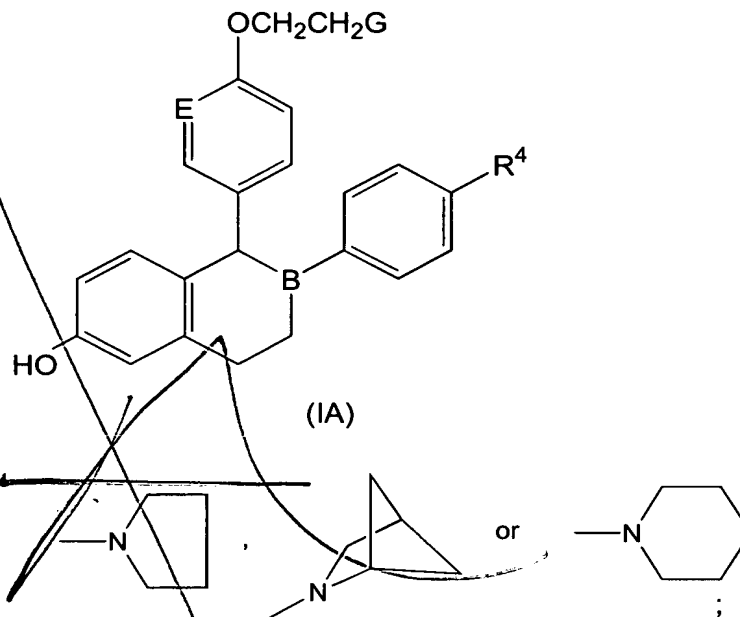
30 p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

3,17 ≈

32. A pharmaceutical composition as in claim 31 wherein said estrogen agonist / antagonist is a compound of formula (IA):



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R⁴ is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

4,18 ≈

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33. A pharmaceutical composition as in claim 32 wherein said estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

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34. A pharmaceutical composition as in 33 wherein said estrogen agonist / antagonist is in the form of a D-tartrate salt.

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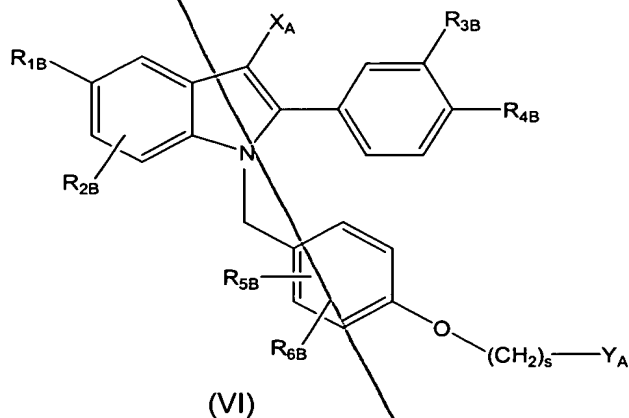
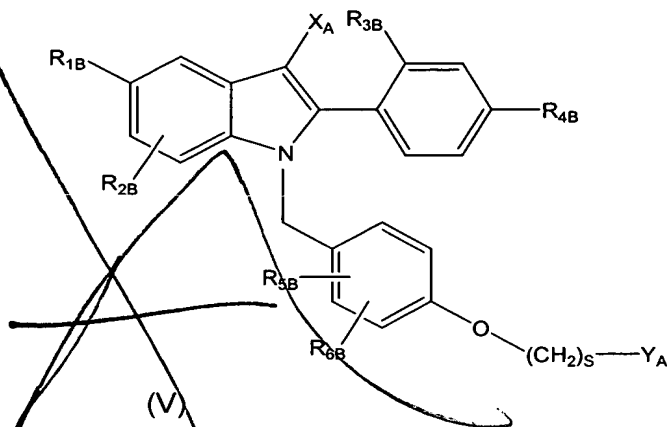
35. A pharmaceutical composition as in claim 29 wherein said estrogen agonist / antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, raloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-

ethoxy]-phenyl)-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604 and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

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7,21 ≈

36. A pharmaceutical composition as in claim 29 wherein said estrogen agonist / antagonist is a compound selected from the formulas V or VI:



15 wherein:

R_{1B} is selected from H, OH, $-O-C(O)-C_1-C_{12}$ alkyl (straight chain or branched), $-O-C_1-C_{12}$ alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers,

R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} are independently selected from H, OH, -O-C(O)-
C₁-C₁₂ (straight chain or branched), -O-C₁-C₁₂ (straight chain or branched or cyclic),
halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl (straight chain or
branched), or trifluoromethyl, with the proviso that, when R_{1B} is H, R_{2B} is not OH;

5

X_A is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, and halogen;

s is 2 or 3,

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Y_A is the moiety:



wherein:

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a) R_{7B} and R_{8B} are independently selected from the group of H, C₁-C₆ alkyl, or phenyl
optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy
(straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; or

20

b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle
containing one nitrogen heteroatom, the heterocycle being optionally substituted with
1-3 substituents independently selected from the group consisting of hydrogen,
hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy,
C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H,
-CN-, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B},
-NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

25

c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle
containing one nitrogen heteroatom, the heterocycle being optionally substituted with
1-3 substituents independently selected from the group consisting of hydrogen,
hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy,
C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H,
-CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B},
-NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

30

d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$, $-CN$, $-CONHR_{1B}$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, $-NHSO_2 R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1 - C_4)alkyl; or

e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$, $-CN$, $-CONHR_{1B}$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, $-NHSO_2 R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1 - C_4)alkyl; or

f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$, $-CN$, $-CONHR_{1B}$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, $-NHSO_2 R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1 - C_4) alkyl; or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

37.

22. A pharmaceutical composition as in claim 25 further comprising a pharmaceutical composition comprising a cyclic guanosine 3',5'-monophosphate elevator.

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38.

11, 25 ~ 23. A pharmaceutical composition as in claim 31 wherein said cyclic guanosine 3',5'-monophosphate elevator is a PDE_v phosphodiesterase inhibitor.

Rule
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59.
~~34.~~

34. A pharmaceutical composition as in claim 33, comprising 1-[[3-(1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxy-phenyl]pyrrolidine-2-carboxylic acid citrate salt

3

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	